Serial No.: 09/812,940

Filed : March 27, 2001

Hargest et al.

Page

: 2

Please replace the paragraph beginning at page 3, line 20 with the following rewritten paragraph:

Att

s Docket No.: 12938-003002

-- In another aspect, carboxylic acid-containing compounds have a structure of formula (I), supra. A is a heteroaryl optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, or amino. Each of X¹ and X², independently, is O or S, and each of Y^1 and Y^2 , independently, is -CH₂-, -O-, -S-, -N(R^a)-, -N(R^a)-C(O)-O-, -O-C(O)-N(R^a)-, -N(R^a)-C(O)-N(R^b)-, -O-C(O)-O-, or a bond; each of R^a and R^b, independently, being hydrogen, alkyl, hydroxylalkyl, or haloalkyl. L is a straight C₃₋₁₂ hydrocarbon chain optionally containing at least one double bond, at least one triple bond, or at least one double bond and one triple bond. The hydrocarbon chain is optionally substituted with C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, or amino, and further optionally interrupted by -O- or -N(R^c)-, where R^c is hydrogen, alkyl, hydroxylalkyl, or haloalkyl.--

Please replace the paragraph beginning at page 12, line 10 with the following rewritten paragraph:

-- The activities of a compound described herein can be evaluated by methods known in the art, e.g., MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay, clonogenic assay, ATP assay, or Extreme Drug Resistance (EDR) assay. See Freuhauf, J.P. and Manetta, A., Chemosensitivity Testing in Gynecologic Malignancies and Breast Cancer 19, 39 – 52 (1994). The EDR assay, in particular, is useful for evaluating the antitumor and antiproliferative activity of a compound of this invention (see Example 28 below). Cells are treated for four days with compound of the invention. Both untreated and treated cells are pulsed with tritiated thymidine for 24 hours. Radioactivity of each type of cells is then measured and compared. The results are then plotted to generate drug response curves, which allow IC₅₀ values (the concentration of a compound required to inhibit 50% of the population of the treated cells) to be determined.--

Please replace the paragraph beginning at page 12, line 25 with the following rewritten paragraph:

H N N (T Serial No.: 09/812,940 Filed : March 27, 2001

Page

: 3

--Histones are isolated from cells after incubation for periods of 2 and 24 hours. The cells are centrifuged for 5 minutes at 2000 rpm in the Sorvall SS34 rotor and washed once with phosphate buffered saline. The pellets are suspended in 10 ml lysis buffer (10 mM Tris, 50 mM sodium bisulfite, 1% Triton X-100, 10 mM magnesium chloride, 8.6% sucrose, pH 6.5) and homogenized with six strokes of a Teflon pestle. The solution is centrifuged and the pellet washed once with 5 ml of the lysis buffer and once with 5 ml 10 mM Tris, 13 mM EDTA, pH 7.4. The pellets are extracted with 2 x 1 mL 0.25N HCl. Histones are precipitated from the combined extracts by the addition of 20 mL acetone and refrigeration overnight. The histones are pelleted by centrifuging at 5000 rpm for 20 minutes in the Sorvall SS34 rotor. The pellets are washed once with 5 mL acetone and protein concentration is quantitated by the Bradford procedure.--

s Docket No.: 12938-003002

Att

Please replace the paragraph beginning at page 13, line 5 with the following rewritten paragraph:

--Separation of acetylated histones is usually performed with an acetic acid-urea

polyacrylamide gel electrophoresis procedure. Resolution of acetylated H4 histones is achieved with 6.25N urea and no detergent as originally described by Panyim and Chalkley, Arch. Biochem. Biophys. 130, 337-346 (1969). 25 µg total histones are applied to a slab gel which is run at 20 ma. The run is continued for a further two hours after the Pyronon Y tracking dye has run off the gel. The gel is stained with Coomassie Blue R. The most rapidly migrating protein band is the unacetylated H4 histone followed by bands with 1,2,3 and 4 acetyl groups which can be quantitated by densitometry. The procedure for densitometry involves digital recording using the Alpha Imager 2000, enlargement of the image using the PHOTOSHOP program (Adobe Corp.) on a MACINTOSH computer (Apple Corp.), creation of a hard copy using a laser printer and densitometry by reflectance using the Shimadzu CS9000U densitometer. The percentage of H4 histone in the various acetylated

states is expressed as a percentage of the total H4 histone.--

